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| EXAMINER | |
|---|---|
| SKIBINSKY, ANNA | |

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| 1631 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/629,351 | GUSTAFSSON ET AL. | |
| | Examiner | Art Unit | |
| | ANNA SKIBINSKY | 1631 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *76-81,101-108 and 120-122* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *76-81,101-108 and 120-122* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/10/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

REQUEST FOR CONTINUED EXAMINATION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/10/2009 has been entered.

Applicants' arguments, filed 3/10/2009 have been fully considered but they are not deemed persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

### *Response to Applicants*

Amendments to claims 76, 79, 101 and new claims 120-122 are acknowledged. Claims 76-81, 101-108 and 120-122 are under examination. Claims 1-75 and 82-100 are cancelled. Claims 109-119 are cancelled.

### *Double Patenting*

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent

and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

**2.** Claims 76-81 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 7-9 and 14 of copending Application No.11/706034 in view of Hellberg et al. Although the conflicting claims are not identical, they are not patentably distinct from each because it

would be obvious to use non-linear terms; e.g. as taught by Hellberg et al. in the sequence activity model in claims 1 and 8 of '034.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Response to Arguments***

Applicants have stated (Remarks, page 5, ¶2) that they will consider the non statutory obviousness-type double patenting rejection when an indication of allowable subject matter is made in either the present application or Application 11/706,034.

A terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) to overcome the instant rejection has not been filed, therefor the rejection is maintained.

***Claim Rejections - 35 USC § 101***

The rejection of claims 79-81 under 35 U.S.C. 101 are withdrawn in view of Applicant's amendments filed 3/10/2009.

***Claim Rejections - 35 USC § 112-2nd paragraph***

1. The rejection of claims 76-78 and 101-108 under 35 U.S.C. 112, second paragraph, are withdrawn in view of Applicant's amendments filed 3/10/2009.

***Claim Rejections - 35 USC § 103***

2. The instant rejection is maintained from the previous Office Action and reiterated herein.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 76-81,101-108, and 120-122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hellberg et al. (Journal of Medicinal Chemistry, vol. 30 (1987) pages 1126-1135) in view of Schellenberger et al. (PGPub 2002/0155460, claiming priority date of 10/10/2000).

1. The instant claims recite a method for identifying amino acid residues for variation in a protein variant library. The identifying entails the characterization of a

training set of protein variant sequences and determining which amino acids in the sequence have the greatest impact on the activity of the sequence.

1. Claim 76(a) recites receiving data characterizing a training set of a protein variant library of systematically varied sequences where the data comprises activity and amino acid sequence for each protein variant in the training set.

2. Hellberg et al. teach the measurement of various properties of amino acids in a peptide (page 1128, col. 1, lines 6-4 from bottom) and data from compounds with known biological activity, a training set, used to construct a model (page 1130, col. 1, lines 3-7 from bottom).

3. Claim 76 (b) recites developing a sequence activity model that predicts activity as a function of amino acid residue type and position in the sequence.

4. Hellberg et al. teach a model constructed from the training set that is used to predict structures that improve biological activity (page 1130, col. 1, lines 1-7 from bottom). The chemical structure is quantified by varying amino acids at certain positions. The structure activity relationship is analyzed with regard to introduction or deletion of features at various positions in the peptides (page 1127, col. 2, lines 6-10 from bottom; page 1128, col. 1, lines 37-45; and col. 2, lines 1-19).

5. Claim 76, step (c) recites ranking positions in a nucleotide sequence or types at specific positions in order of impact on the desired activity.

6. Hellberg et al. teach using the model to quantify peptide analogues where each varied amino acid is described by variables (page1128, col. 2, section "II. Peptide Description"). A test matrix is taught where the amino acid with the highest absolute z

values are chose to be included in a test series (page 1129, col. 2, ¶ 7 and Table V) and shows a test series of 16 peptides with four amino acid positions that were varied.

7. Claim 76, step (d) recites using the ranking to identify one or more nucleotides, in the reference nucleotide sequence that are to be varied or fixed in order to impact the desired activity.

8. Hellberg et al. teach varying positions 2 and 4 in Pepstatin Analogues (Example III, page 1133, col. 1) wherein the calculated activity of seven analogues are plotted as function of activity in Figure 3.

9. Claim 76(e) recites generating on or more of the protein variants encoded by the reference nucleotide sequence with the identified nucleotides that are varied or fixed.

10. Hellberg et al. teach generating the analogues having the identified amino acid residues varied in order to impact desired activity, as shown in Figure 3. Furthermore, Hellberg et al. teach the design a series of analogues based on the analysis done with the activity model (page 1128, col. 1., lines 45-49; and page 1129, col. 2, section "Design Example").

2. As in claim 77, Hellberg et al. further teach that their model is not limited to amino acid sequences but that a design for only coded amino acids, a set of codon sequences (i.e. nucleotides in DNA) can be constructed that corresponds to a set of designed peptide fragments (page 1135, col. 2, ¶2).

3. Hellberg et al. teach performing steps (a)-(c) using activity and sequence data from protein variants, page 1135, col 2, ¶ 2), as in claim 107.

4. Hellberg et al. teach partial least square regression (PLS) (Abstract and page 1130, col. 1, ¶ 2-3), as required in claims 120-121.

5. Hellberg et al. teach principal component regression (PCA) (page 1127, Table II, caption and ¶ 1), as required in claim 122.

6. Hellberg et al do not teach generating a new protein variant library, assaying the new protein library to develop a new computational algorithmic sequence activity model and using the new model to identify nucleotides in a reference sequence that are to be varied as in claim 76, steps (e) to (g). Hellberg et al. using a computer program product to carryout the steps of the method, as in claims 79-81. Hellberg et al. do not teach a library of protein mutants generated from nucleic acid sequences and using directed evolution methods such as gene synthesis, mutagenesis, and recombination-based screening where nucleotide sequences are used to generate protein libraries based on the prediction of the activity model, as in claims 78, 101-106 and 108.

7. Claim 76, step (e) recites generating a new protein variant library containing at least one of the protein variant in which the identified nucleotides are varied or fixed to impact desired activity.

8. Schellenberger et al. teach a "probability matrix' (another form of sequence activity model) that provides an estimate that a given residue will provide a desired activity in a biological polymer (e.g. polynucleotide) of interest (par. [0059]) and constraint vectors that reflect the likelihood that a specific mutation at each amino acid position of a protein will improve or effect the desired activity (par. [0073]). Schellenberger et al. also teach ranking amino acids (par. [0065])

9. Schellenberger et al. teach construction of libraries by randomizing codons at specific locations that have been identified (par. [0087] to [0090]).

10. Claim 76, step (f) recites assaying the new protein variant library to provide activity information used to develop a new computational algorithmic sequence activity model.

11. Schellenberger et al. teach generating a library and screening the library of proteins for members with desired activity and deriving information from the screening which is then used to design an improved probability matrix and constraint vectors (i.e. develop a new computational algorithmic sequence activity model) for a next iteration of mutagenesis and library construction (par. [0099]).

12. Claim 76, step (g) recites using the new computational algorithmic sequence activity model to identify one or more nucleotides in a new reference nucleotide sequence that are to be varied or fixed in order to impact the desired activity.

13. Schellenberger et al. teach the iteration of their method using a new activity model, wherein their activity model is the probability matrix and constraint vectors which estimates that a given residue will provide a desired activity in a biological polymer (e.g. polynucleotide) of interest (par. [0059]) and constraint vectors that reflect the likelihood that a specific mutation at each amino acid position of a protein will improve or effect the desired activity (i.e. identify one or more nucleotides in a new reference nucleotide sequence that are to be varied or fixed in order to impact the desired activity).

14. Schellenberger et al. teach that molecules with desired activity can be propagated and subjected to rounds of mutagenesis and selection (par. [0008]).

Schellenberger et al. generating libraries of molecules including nucleic acids by expressing in host cells and screening molecules for desired properties, as in claim 78.

15. Schellenberger et al. teach the use of computers (i.e. Computer program product) to carryout sequence activity calculations for determining which residue will provide a desired activity in a biological polymer (e.g. polynucleotide) of interest, (par. [0066], [0071], and [0080]), as required in claims 79-91.

16. Schellenberger et al. teach construction of libraries by randomizing codons at specific locations that have been identified (par. [0087] to [0090]), generating libraries of proteins from the nucleic acid sequences and screening the libraries of proteins for members with desired activity (par. [0099]), as in claim 101.

17. Schellenberger et al. teach mutation of genes to diversify polymeric biological molecules and create a library of genes used to express proteins (par. [0005] to [0006]), as in claim 102.

18. Schellenberger et al. teach mutagenesis (par. [0006]), as in claim 103.

19. Schellenberger et al. teach recombination-based diversity generation mechanism (par. [0007]), as in claim 104.

20. Schellenberger et al. teach further screening of newly generated protein variant library to identify variants having desired activity (Abstract, par. [0012], [0035], [0099]), as in claim 105.

21. Schellenberger et al. teach sequencing the library (par. [0099]) ad using sequence information to introduce diversity into a protein of interest (par. [0007]), and

characterizing the sequence (par. [0021]) and PCR for sequencing (par. [0094]), as in claim 106.

22. Schellenberger et al. teach codon based mutagenesis (par. [0087]) and a codon by codon technique using mixtures of activated trinucleotides at the positions to be substituted (par. [0091]), as in claim 108.

23. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have implemented the sequence activity model (i.e. QSAR) of Hellberg et al. to in the iterative method for generating a protein variant library with the as taught by Schellenberger et al. One of ordinary skill in the art would have been motivated to use the activity model of Hellberg et al. with the method of creating libraries of biological polymers as taught by Schellenberger et al. because Schellenberger et al teach the need for synthetically screening possible permutations in a polymeric biological molecule such as a polynucleotide (par. [0004]). One of skill in the art would have had a reasonable expectation of success at utilizing the structure activity model of Hellberg et al. with the generation of protein libraries using expression of protein sequences via gene synthesis, mutagenesis and recombination as taught by Schellenberger et al. because Schellenberger et al. also teaches the use of QSARs (par. [0104]).

***Response to Arguments***

1. Applicant's arguments filed 3/10/2009 have been fully considered but they are not persuasive.

2. Applicants argue (Remarks, page 7, ¶2-3) that Schellenberger et al. does not teach limitation (f) of claim 76, wherein Schellenberger's model is simply probability information specific to individual residues that are present in the probability matrix which represents that the probability that a polymer will have a desire activity in a particular residue is found in that position. Applicants further argue that the teaching of Schellenberger et al. falls short of a computational algorithmic sequence activity model that estimates activity for an entire sequence.

3. In response, Schellenberger et al. do teach the limitation of claim 76, step (f) because they teach generating a library and screening (i.e. assaying) the library of proteins for members with desired activity and deriving information (i.e. an update training set) which is then used to design an improved probability matrix and constraint vectors (i.e. develop a new computational algorithmic sequence activity model) for a next iteration of mutagenesis and library construction (par. [0099]).

4. The instant claim does not require that sequence activity model must "estimate activity for an entire sequence," as argued by Applicants. However, even as Applicants themselves have noted, the activity matrix of Schellenberger et al. estimates the "probability that incorporation of the residue in that column at the position in that row will produce a polymer having the desired activity" (par. [0060]). Therefore, because Schellenberger et al. teaches estimating probability for a desired activity of a polymer, this is equivalent to teaching estimating activity for an entire sequence (a polymer is an entire sequence).

5. Applicants argue (Remarks, page 8, ¶1-2) the merits of Schellenberger's probability matrix and that Schellenger et al. does not teach that activities of new library members can be calculated from the constraint vector or probability matrix.

6. In response, Although Schellenberger et al. do teach QSARs (i.e. a sequence activity model), however Heller et al. is relied up to teach a sequence activity model to meet the limitations of claim 76, steps (a)-(d). Heller et al. do not teach not teach generating a new protein variant library, assaying the new protein library to develop a new computational algorithmic sequence activity model and using the new model to identify nucleotides in a reference sequence that are to be varied as in claim 76, steps (e) to (g). Therefor, Schellenberger et al. is relied upon to teach the iterative aspect of the method wherein a new sequence activity model is generate as a result of information from real proteins derived from the initial sequence activity model, as recited in steps (e) to (g). Schellenger et al. do teach generating a library and screening the library of proteins for members with desired activity and deriving information from the screening which is then used to design an improved probability matrix and constraint vectors (i.e. develop a new computational algorithmic sequence activity model) for a next iteration of mutagenesis and library construction (par. [0099]).

7. Applicants argue (Remarks, page 9, ¶1)that Schellenberger et al. mentions QSAR techniques but there is nothing to suggest that Schellenberger's use of QSAR is pertinent to Hellberg et al.

8. In response, Schellenberger et al. teach that statistical analyses of the correlation between structures and functions of molecules have been widely used to guide the

optimization of small molecule drugs (quantitative structure activity relationship, or QSAR). Therefore, the matrix taught by Schellenberger et al. fall under what Schellenberger et al. describe as a QSAR (par. [0104]).

9. Applicants argue that a skilled artisan would not be motivated to combine the art of Heller et al. with that of Schellenberger et al. (Remarks, page 9, ¶2-3).

10. In response, Heller et al. is relied up to teach the generating of an initial sequence activity model to meet the limitations of claim 76, steps (a)-(d). Schellenger et al. is relied upon to teach the iterative process of using a sequence activity model to generate a protein libriary, assay the new protein library to develop a new computational algorithmic sequence activity model (as in step (b)) and using the new model to identify nucleotides in a reference sequence that are to be varied (as in steps (c)-(d)), as in claim 76, steps (e) to (g). Therefor, Schellenberger et al. is relied upon to teach the iterative aspect of the method wherein a new sequence activity model is generate as a result of information from real proteins derived from the initial sequence activity model, as recited in steps. Schellenger et al. do teach generating a library and screening the library of proteins for members with desired activity and deriving information from the screening which is then used to design an improved probability matrix and constraint vectors (i.e. develop a new computational algorithmic sequence activity model) for a next iteration of mutagenesis and library construction (par. [0099]).

11. It would have been prima facie obvious to one of ordinary skill in the art to have used the sequence activity model taught by Heller et al. in the iterative manner taught by in the method of Schellenberger et al. One of ordinary skill in the art would have

been motivated to use the activity model of Hellberg et al. with the method of creating libraries of biological polymers as taught by Schellenberger et al. because Schellenberger et al. teach the need for synthetically screening possible permutations in a polymeric biological molecule such as a polynucleotide (par. [0004]).

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anna Skibinsky whose telephone number is (571) 272-4373. The examiner can normally be reached on 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lori A. Clow, PhD/
Primary Examiner, Art Unit 1631 signing for

Anna Skibinsky, PhD
Art Unit 1631